Strategic Partnering to Evaluate Cancer Signatures

The National Cancer Institute (NCI) invites investigators to form strategic partnerships that will bring together the multidisciplinary expertise and resources needed to determine how the information derived from comprehensive molecular analyses can be used to improve patient care and, ultimately, patient outcomes. The purpose of this request for applications (RFA) is to build on recent demonstrations that molecular signatures correlate with important clinical parameters in cancer. Applicants are asked to propose evaluation of potential clinical usefulness of molecular signatures already developed using a variety of molecular analysis technologies including DNA-, RNA-, or protein-based technologies.

Retrospective studies have shown that molecular signatures have identified subgroups of patients whose tumors are histopathologically the same but who have different clinical outcomes. The challenge is to translate the information in these molecular signatures into tools that can be used in clinical decision making. To meet this challenge, signatures must be confirmed in independent studies. Critical elements of signatures that correlate most strongly with the clinical end point of interest must be identified and confirmed. Robust assays feasible for use in the clinical setting must be developed and validated.

This open competition will provide the cancer research community the opportunity to establish collaborations focused on the translation of promising molecular profiles toward clinical applications. The NCI will continue the policy of requiring public release in a timely fashion of the rich data sets generated during these projects. Access to these data sets will benefit the entire cancer research community. This initiative will help ensure that the NCI goal of eliminating the suffering and death from cancer by 2015 is met.

The ability of molecular profiles to provide useful clinical information is being demonstrated in many projects throughout the cancer research community and must be evaluated further. Scientists are discovering molecular signatures by analysis of gene expression at the RNA level, gene expression following protein translation, gene mutations, DNA deletions, DNA amplifications, epigenetic changes of DNA, and post-translational modification of proteins. The challenge is to move beyond the initial discovery of potentially useful profiles, to decide what subset of the elements in the profiles needs to be measured, to confirm that the profiles are robust and can be reproducibly measured, and to evaluate the clinical utility of the profiles.

This RFA is intended to support projects carrying out the extensive research needed to bridge the gap between discovery of molecular profiles and their integration into clinical decision making. Collaborations must be established to provide all of the expertise and clinical resources required to achieve proposed project goals. It is anticipated that these will be multi-institutional projects involving investigators with expertise in technology development and application, cancer biology, oncology, pathology, clinical cancer research, biostatistics, bioinformatics, and, possibly, biomedical imaging.

Applicants must propose projects that build on previously identified molecular profiles. Applications proposing only profile discovery or technology development projects will not be considered responsive to this RFA. The proposed studies should be designed to confirm and refine signatures that have been demonstrated to provide information that is potentially useful clinically and that may be used to aid in making clinical decisions.

Applicants may propose to define critical components in the signature, to confirm that the selected components continue to provide the desired clinical information, and to develop robust assays for measuring those components. They may continue to develop and/or modify analytical technologies and algorithms for data analysis required to meet the goals of the proposed projects.

Applicants should propose projects that address clinical issues or needs in a specific cancer or a closely related set of cancers or in a group of patients whose cancers have related molecular alterations. Applicants must describe the clinical question(s) or need(s) they plan to address. Examples of questions of interest may include, but are not limited to, risk of progression in early-stage disease, prognosis at the time of diagnosis, identification of subsets within a tumor stage or grade where there is known heterogeneity in clinical behavior including differential response to standard therapies and/or radiation response, and selection of appropriate patients for or prediction of response to selected or targeted therapies. Applicants should not propose projects addressing early detection of cancer in asymptomatic or high-risk populations or risk of progression of premalignant lesions.

Applicants may propose the use of a variety of analytical platforms. Applicants may evaluate signatures that have previously been identified using analytical technologies such as gene expression microarrays, SAGE, multiplex PCR, or any of a large number of protein analysis technologies. Genomic analysis technologies such as array CGH, comprehensive mutational analysis technologies, SNP analysis, and analysis of epigenetic events are also appropriate. Applicants must demonstrate that they have experience with the analytical technologies that will be used in the project and demonstrate that the technologies can be used for analysis of standard pathological specimens. Applicants are encouraged to propose the use of multiple analytical strategies. The integration of data to build clinically useful profiles that can be measured reproducibly in a clinical setting must be the focus of the project, no matter which technologies or analytic platforms are proposed.

The confirmation, refinement, and evaluation of clinically useful molecular profiles and the development of robust clinical assays are the primary goals of this initiative. Clinical utility of the signatures and performance of the clinical assays in the context of their intended clinical use must be validated before they can be integrated into clinical practice. Final validation of the profiles in a clinical trial setting is beyond the scope of this RFA. However, it is anticipated that some of the projects may be ready to move profiles into clinical trials as early as the midpoint of the project period. NCI staff will facilitate collaborations between the projects funded on this initiative and other clinical resources and clinical trials activities supported by the NCI.

Applicants must justify the numbers of specimens to be analyzed based on appropriate statistical designs for the proposed studies. Applicants must have established collaborations to ensure availability of the clinical materials required. The availability of tissue resources with appropriate clinical annotation is critical to the successful completion of the projects. Experience has demonstrated that the dimensionality of the molecular profiling data requires the analysis of hundreds of specimens to get statistically significant results. Applicants may propose to obtain tissues from a previous collection or prospectively, as long as the specific aims proposed can be accomplished within the period of the grant award.

Applicants should request sufficient resources for their bioinformatics staff to be able to provide an appropriate interface with the NCI Center for Bioinformatics. Sharing of the data between projects where appropriate and public release of data after publication will be a requirement for this initiative. Awardees will retain primary rights to the data developed under these awards, subject to government rights of access consistent with current DHHS, PHS, and NIH policies.

This RFA uses just-in-time concepts. It also uses the nonmodular budgeting formats. Follow the instructions for nonmodular budget research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

This RFA will use the NIH cooperative agreement (U01) award mechanism. Applicants are solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Applications that are not funded in the competition described in this RFA may be resubmitted as new investigator-initiated applications using the standard receipt dates for new applications described in the instructions to the PHS 398 application.

The NCI intends to commit approximately $10 million in fiscal year 2004 to fund 3–4 new grants in response to this RFA, contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. An applicant may request a project period of up to 5 years and a budget for total direct costs of up to $2.5 million per year. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Applicant institutions may be for-profit or nonprofit organizations; public or private institutions, such as universities, colleges, hospitals, and laboratories; units of state and local governments; eligible agencies of the federal government; or domestic or foreign institutions/organizations. Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his/her institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

In order to ensure maximum progress in the projects funded by this initiative and to maximize progress toward the NCI 2015 goals, several special activities will be required of funded investigators. An annual meeting of all funded investigators will be held to share progress and research insights that may benefit all of the projects. The annual scientific meeting will be initiated after the first year of funding. Other focused meetings will be held each year to address arising issues or to take advantage of special scientific opportunities. Applicants should request travel funds in their budgets for key personnel to attend two meetings per year.

Funded investigators will be asked to work together on issues common to all funded projects. Although each applicant will propose an independent project, all applicants are expected to face many of the same challenges and will benefit from the experiences of and interactions with the other funded investigators. The interactions of funded groups will be overseen by a steering committee made up of two investigators, the principal investigator, one additional investigator from each funded project, and appropriate NCI staff. Applicants should state in their applications their commitment to participating on the steering committee and in interactions among the funded groups.

When proposed studies involve collection of human samples, specimens and/or clinical data, investigators should consult the NIH brochure titled *Research on Human Specimens: Are You Conducting Research Using Human Subjects?* (http://www-cdp.ims.nci.nih.gov/policy.html) and in the OHRP guidance on repositories, tissue storage activities, and data banks (http://ohrp.osophs.dhhs.gov/g-topicstest.htm) to

ensure appropriate protection of human subjects in research.

Applicants must describe how they intend to meet NIH policies for sharing of data or why data sharing is not possible. In this regard, attention is drawn to the NIH Final Statement on Sharing Research Data (http://grants.nih.gov/grants/policy/data_sharing/index.htm and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html), which was published in the NIH Guide on 26 February 2003 ("Data Sharing Guidelines").

A meeting of interested investigators will be held 14 May 2004 in the Natcher Conference Center at NIH, Bethesda, Maryland. The meeting is intended to answer questions potential applicants may have about the intent of the initiative. Prospective applicants are asked to submit a nonbinding letter of intent by 22 June 2004. The anticipated award date is 1 April 2005.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a Dun and Bradstreet Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for federal grants or cooperative agreements. The DUNS number can be obtained by calling 1-866-705-5711 or through the website at http://www.dunandbradstreet.com/. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance, contact GrantsInfo, 301-435-0714, e-mail: GrantsInfo@nih.gov.

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Revolutionary Genome Sequencing Technologies: The $1,000 Genome

The purpose of this request for applications (RFA) is to solicit grant applications to develop novel technologies that will enable extremely low-cost genomic DNA sequencing. Current technologies are able to produce the sequence of a mammalian-sized genome of the desired data quality for $10–50 million; the goal of this initiative is to reduce costs by at least 4 orders of magnitude, so that a mammalian-sized genome could be sequenced for approximately $1,000. Substantial fundamental research is needed to develop the scientific and technological knowledge underpinning such a major advance. Therefore, it is anticipated that the realization of the goals of this RFA is a long-range effort that is likely to require as much as 10 years to achieve. The parallel RFA HG-04-002 (details at http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-04-002.html) solicits grant applications to develop technologies to meet the shorter-term goal of achieving a 2 orders of magnitude cost reduction in about 5 years.

The ability to sequence complete genomes and the free dissemination of the sequence data have dramatically changed the nature of biological and biomedical research. Sequence and other genomic data have the potential to lead to remarkable improvements in many facets of human life and society, including the understanding, diagnosis, treatment, and prevention of disease; advances in agriculture, environmental science, and remediation; and the understanding of evolution and ecological systems.

At current prices, the cost of sequencing a mammalian-sized genome means we must still be very selective when choosing new genomes to sequence. In particular, we remain very far away from being able to afford to use comprehensive genomic sequence information in individual health care. For this and many other reasons, the rationale for achieving the ability to sequence entire genomes very inexpensively is very strong.

Given the broad utility and high importance of dramatically reducing DNA sequencing costs, the National Human Genome Research Institute (NHGRI) is launching two parallel technology development programs. For both programs, the cost targets are defined in terms of a mammalian-sized genome, about 3 gigabases (Gb), with a target sequence quality equivalent to, or better than, that of the mouse assembly published in December 2002 [Nature 420:520 (2002)].

The ultimate goal of this program is to obtain technologies that can produce an assembled sequence (i.e., *de novo* sequencing). However, an accompanying shorter-term goal is to obtain highly accurate sequence data at the single base level, i.e., without assembly information, that can be overlaid onto a reference sequence for the same organism (i.e., resequencing). This could be achieved, for example, with short reads that have no substantial information linking them to other reads. While the sequence product of this kind of technology would lack some important information, such as information about genomic rearrangements, it would nevertheless potentially be available more rapidly and produce data of great value for certain uses in studying disease etiology and in individualized medicine. Therefore, both programs' objectives include a balanced portfolio of projects developing both *de novo* and resequencing technologies.

The goal of research supported under this RFA is to develop new or improved technology to enable rapid, efficient genomic DNA sequencing. New sensing and detection modalities will likely be needed to achieve these goals. New fabrication technologies may also be required. It is therefore anticipated that proposals responding to this RFA will need to involve fundamental and engineering research conducted by multidisciplinary teams of investigators. The guidance for budget requests accommodates the formation of groups having investigators at several institutions, in cases where that is needed to assemble a team of the appropriate balance, breadth, and experience.

Although the ultimate goal is to develop full-scale sequencing systems, independent research on essential components will also be considered responsive to this RFA. However, it will be important for applicants proposing research on system components or concepts to describe how the knowledge gained as a result of their project would be incorporated into a full system that they might subsequently propose to develop, or that is being developed by other groups. Such independent proposals are an important path for pursuing novel high-risk/high-payoff ideas.

Research conducted under this RFA may include development of the computational tools associated with the technology, e.g., to extract sequence information, including signal processing, and to evaluate sequence quality and assign confidence scores. It may also address strategies to assemble the sequence from the information being obtained from the technology or by merging the sequence data with information from parallel technology. However, this RFA will not support development of sequence assembly software independent of technology development to obtain the sequence.

The quality of sequence to be generated by the technology is of paramount importance for this solicitation. Two major factors contributing to genomic sequence quality are per-base accuracy and contiguity of the assembly. Much of the utility of comparative sequence information will derive from characterization of sequence variation between species, and between individuals of a species. Therefore, per-base accuracy must be high enough to distinguish polymorphism at the single-nucleotide level (substitutions, insertions, deletions). Experience and resulting policy have established a target accuracy of not more than 1 error per 10,000 bases. All applications in response to this RFA, whether to develop resequencing or *de novo* sequencing technologies, must propose achieving per-base quality at least to this standard.

The NHGRI intends to commit approximately $6 million in fiscal year 2004 to fund 3–10 new and/or competitive continuation grants in response to this RFA, and an additional $5 million in fiscal year 2005. For the R21 mechanism, an applicant may request a project period of up to 3 years and a budget of up to $200,000 in direct costs per year. For R21/R33 applications, the total project period may not exceed 5 years, distributed as required for the project; the R21 phase may request a budget up to $200,000 in direct costs and the R33 phase up to $2 million in direct costs per year. For R01 and P01 mechanisms, an applicant may request a project period of up to 5 years and a budget of up to $2 million in direct costs per year. Budgets may exceed this guidance only to accommodate indirect costs to subcontracts. Applicants should be aware that the NHGRI intends to fund as many promising projects, of varying scope, as possible in order to pursue multiple approaches to solving these difficult problems and mitigate risk. Therefore, awards may not be made at the maximum budget level.

Applicant institutions may be for-profit or nonprofit organizations; public or private institutions, such as universities, colleges, hospitals, and laboratories; units of state and local governments; eligible agencies of the federal government; or domestic or foreign institutions/organizations. Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his/her institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

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Letters of intent must be received by 15 March 2004 or 14 September 2004. Applications are due 15 April 2004 or 14 October 2004. The earliest anticipated start date is 30 September 2004 or 1 June 2005.

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